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Cascade cyclization intermolecular dipolar cycloaddition by multi-component couplings—synthesis of indolizidines and pyrrolizidines

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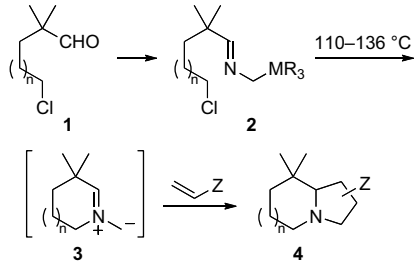
ABSTRACT

A three-component coupling reaction of a primary amine (an amino-acid or amino-ester or hydroxylamine), an alkene or alkyne dipolarophile and an aldehyde bearing a halide as a leaving group has been developed. Condensation of the amine with the aldehyde and cyclization (intramolecular N-alkylation) provides, after decarboxylation or deprotonation, a cyclic azomethine ylide (or nitrone) that undergoes intermolecular dipolar cycloaddition with the dipolarophile. This sets up, in a single step, the bicyclic indolizidine or pyrrolizidine ring system, depending on the length of the tether between the aldehyde and the halide. The reaction is successful with stabilized and non-stabilized azomethine ylides that result from using primary amino-esters or amino-acids, respectively.

The dipolar cycloaddition reaction of azomethine ylides provides a convenient method to access substituted pyrrolidines, dihydropyrroles and pyrroles.[1–6] Various methods can be used to generate the azomethine ylide, and many intermolecular examples using activated dipolarophiles (typically alkenes or alkynes bearing electron-withdrawing groups) have been reported. The chemistry can be applied to bicyclic products using intramolecular cycloadditions, in which the dipolarophile is tethered to the azomethine ylide.[7–24] An alternative way to access bicyclic products was reported by Pearson and co-workers, in which a cyclization generates the azomethine ylide that undergoes intermolecular cycloaddition with a dipolarophile.[25] In this chemistry, the aldehydes **1** were treated with (tributylstannyl)methylamine or (trimethylsilyl)methylamine to give the imines **2** (Scheme 1). Heating with the dipolarophile promoted cyclization and demetalation to give the azomethine ylides **3**, which undergo cycloaddition to the bicyclic amines **4**.

Recently, we used this type of chemistry in an intramolecular cycloaddition to give three rings in a single transformation and applied it to the total synthesis of several *Aspidosperma* alkaloids.[26] In this work, we found that simple amino-acids or amino-esters could be used in place of the stannyl- or silyl-methylamines. This has advantages as it avoids the use of the metal species and allows ready access to different substituted products by using readily available amino-acid starting materials. We therefore considered whether the cyclization—intermolecular cycloaddition chemistry would be amenable to using amino-acids or esters. We report here the successful demonstration of this chemistry.



Scheme 1. Pearson's cyclization–cycloaddition chemistry.[3] n = 1–3; MR_3 = $SnBu_3$ or $SiMe_3$; Z = electron-withdrawing group.

The aldehyde **1** (n = 1) was prepared by a method that was slightly different from that used by Pearson and co-workers.[25] In our case, we alkylated the commercially available isobutyronitrile with LDA and 1-bromo-3-chloropropane and then reduced the nitrile **5**, n = 1, with DIBAL-H (Scheme 2). This method was unsuitable for the analogue **1**, n = 0 and it was better to alkylate isobutyronitrile with 2-bromoethyl-trimethylsilyl ether followed by desilylation with HCl to give the intermediate alcohol that was converted to the chloride **5** (n = 0) with *N*-chlorosuccinimide (NCS) and PPh_3. Reduction with DIBAL-H then gave the aldehyde **1**, n = 0.

Heating the aldehyde **1**, n = 1, with glycine and a selection of dipolarophiles in toluene for 24 h resulted in the formation of the desired cycloadducts **6**–**10** (Scheme 3, Table 1, Fig. 1). The best

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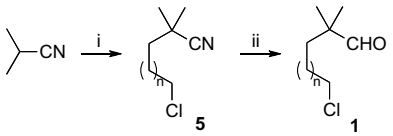
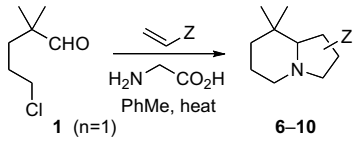


Scheme 2. Preparation of the aldehyde **1**; Reagents and condition: (i) For $n = 1$: LDA, THF, −78 °C, then $ClCH_2CH_2CH_2Br$, 86%; or for $n = 0$: LDA, THF, −78 °C, then $TMSOCH_2CH_2Br$, 98%, then HCl, room temperature, 86%, then NCS, PPh_3, THF, 81%; (ii) DIBAL-H, CH_2Cl_2, $n = 1$: 88%, $n = 0$: 56%.



Scheme 3. Cyclization/cycloaddition of **1**, $n = 1$, with glycine.

Table 1
Yields for reaction of aldehydes **1** with glycine

1, *n*	Dipolarophile CH_2=CHZ	Product[a]	Yield	dr
1	*N*-Methylmaleimide	**6**	70	1:1
1	*N*-Phenylmaleimide	**7**	63	1:1
1	Dimethyl maleate	**8**	63	1:1
1	Phenyl vinyl sulfone	**9**	53	1.5:1:1:1
1	Methyl acrylate	**10**	66	2:1.5:1:1
0	*N*-Methylmaleimide	**11**	48	1:1
0	Dimethyl maleate	**12**	52	1:1

[a] See Figure 1.

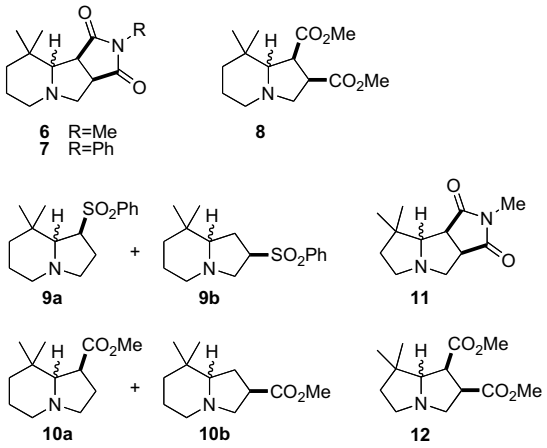
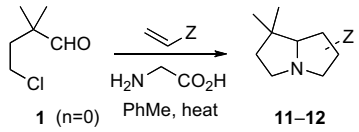


Figure 1. Structures of cycloadducts **6**–**12**.

yields were obtained using an excess (4 M equiv) of glycine and a slight excess (1.5 M equiv) of the dipolarophile. No products were isolated when heating using a microwave or using THF or water as the solvent. With symmetrical dipolarophiles, a mixture of two stereoisomers of the indolizidine ring products (**6**–**8**) was formed without any selectivity. With unsymmetrical dipolarophiles, a mixture of regio- and stereoisomers was obtained (**9** and **10**).

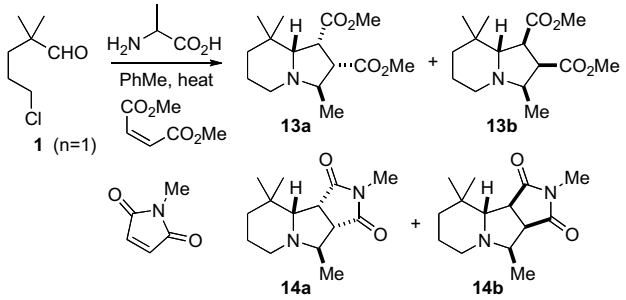
Cyclization/cycloaddition of the aldehyde **1**, $n = 0$, was also attempted with glycine and various dipolarophiles and resulted in the formation of the pyrrolizidine ring products **11** and **12** (Scheme 4, Table 1, Fig. 1). As before, a mixture of isomeric products was formed.



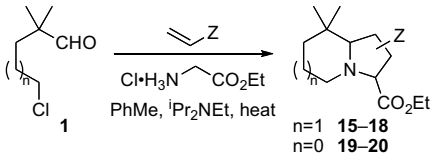
Scheme 4. Cyclization/cycloaddition of **1**, $n = 0$ with glycine.

We next attempted cycloadditions with alanine (Scheme 5). Suprafacial cycloaddition onto cis-disubstituted dipolarophiles (dimethyl maleate and *N*-methylmaleimide) could give rise to four possible stereoisomeric products. However, only two stereoisomers were obtained in each case. Previously, the reactions with glycine (Scheme 3) gave two stereoisomers; it is likely therefore that the methyl substituent α- to the nitrogen atom prefers one of the two configurations (i.e., cycloaddition through the S- or W-shaped azomethine ylide). Using ^{1}H NMR COSY and NOESY (plus coupling constants), we were able to determine that the cycloadducts from reaction with *N*-methylmaleimide had the structures **14a** and **14b**. These arise from cycloaddition through the S-shaped azomethine ylide. The stereochemistry of the cycloadducts **13a** and **13b** is assumed, based on the expected preference for cycloaddition through the S-shaped ylide.

Heating the aldehydes **1** ($n = 1$ or 0) with glycine ethyl ester and various dipolarophiles in the multi-component cyclization/cycloaddition for 18–24 h provided the expected bicyclic and tricyclic amine products **15**–**20** (Scheme 6, Table 2, Fig. 2). Of the four possible stereoisomeric products **15**, only three stereoisomers



Scheme 5. Cyclization/cycloaddition with alanine; for dimethyl maleate, 51%, dr 1.2:1; for *N*-methylmaleimide, 52%, dr 1.3:1 (**14a**:**14b**).



Scheme 6. Cyclization/cycloaddition with glycine ethyl ester.

Table 2
Yields for reaction of aldehydes **1** with glycine ethyl ester

1, *n*	Dipolarophile	Product[a]	Yield	dr
1	*N*-Methylmaleimide	**15**	94	2.2:2:1
1	Dimethyl maleate	**16**	74	2.5:1:1
1	Methyl acrylate	**17**	77	3.4:2.4:1
1	DMAD	**18**	45[b]	1:0
0	*N*-Methylmaleimide	**19**	73	7:2:1
0	Dimethyl maleate	**20**	62	15:2:1

[a] See Figure 2.
[b] Cycloaddition at room temperature.

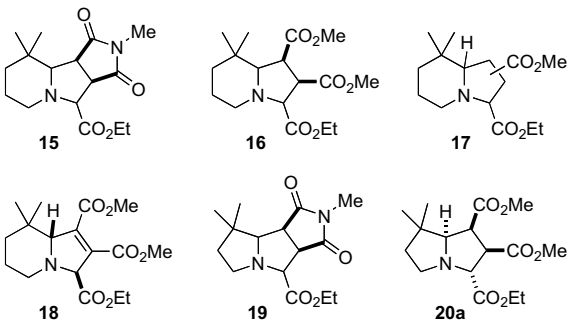


Figure 2. Structures of cycloadducts **15**–**20**.

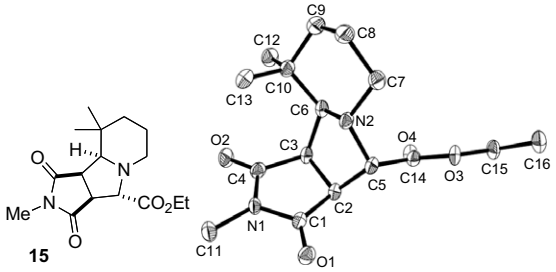
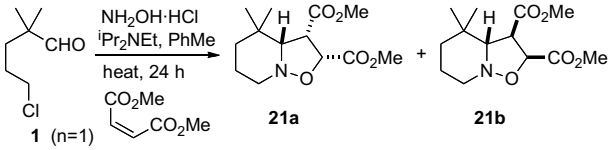


Figure 3. X-ray crystal structure of the major isomer of compound **15**.

(separable) were obtained. The major stereoisomer was crystalline, and X-ray crystal structure analysis revealed that the product was the stereoisomer shown in Figure 3. This is the *endo* adduct from the S-shaped ylide, although two other stereoisomers were formed in similar amounts.

The major isomer **17** in the cycloaddition with methyl acrylate was separable, and ^{1}H NMR spectroscopy suggested that it was the 2,4-diester regiochemistry resulting from *endo* addition. To avoid products from conjugate addition, cycloaddition with dimethyl acetylene dicarboxylate (DMAD) was best carried out by heating the aldehyde **1**, $n = 1$, with glycine ethyl ester at 60 °C for 2 h then cooling to room temperature and addition of DMAD. This gave the dihydropyrrole product **18** as a single stereoisomer (determined by ^{1}H NMR NOESY). Cycloadditions to give the pyrrolizidine ring systems **19** and **20** were particularly selective in favour of one major stereoisomer (Table 2, $n = 0$). In line with the previous examples, the major isomer for compound **20** was found (by ^{1}H NMR NOESY) to arise from the S-shaped ylide and endo preference (structure **20a**). Separation of the isomers was possible by column chromatography, and compound **20a** was isolated in 52% yield.

In addition to the above, we have carried out the cyclization/cycloaddition sequence using hydroxylamine. This gives the intermediate oxime and, after cyclization, the nitrone. Intermolecular dipolar cycloaddition of **1** ($n = 1$) with dimethyl maleate gave the cycloadducts **21** (Scheme 7). The stereoisomers were separable, and ^{1}H NMR NOESY indicated that the major stereoisomer was compound **21a** (the expected endo adduct).



Scheme 7. Cyclization/cycloaddition with hydroxylamine; 77%, dr 1.6:1.

In summary, we have demonstrated that various amines can be added to the aldehydes **1** ($n = 1$ or 0) to generate cyclic 1,3-dipoles that undergo intermolecular cycloaddition with activated dipolarophiles. The amines glycine, alanine, glycine ethyl ester and hydroxylamine all reacted successfully. The chemistry provides an efficient multi-component synthesis of substituted indolizidines and pyrrolizidines. Further examples, including other types of aldehyde substrates, are currently under investigation and will be reported in due course.

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